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THE INCREASE OF LUNG CANCER: HISTORICAL PERSPECTIVE

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Introduction

The progressive rise in the incidence of bronchogenic carcinoma has fostered the concept that this is a modern disease produced by environmental influences. In the zealous search for etiologic agents many basic facts have been disregarded. Primary cancer of the lung was recognized more than 150 years ago and was prevalent during an era far removed from present carcinogenic considerations.

The phenomenon of accelerated increase of a disease coincident with improved diagnostic techniques has occurred many times in the course of medical history. In England, at the turn of the century, the marked rise in cancer deaths was attributed variously to polluted water, parasitic infestation, consumption of meat, and excessive rainfall, the last showing a high degree of statistical correlation. Newsholme, the health officer at Brighton, observed prophetically that when a cancer became diagnostically accessible the incidence automatically increased.

The interpretation of cancer mortality rates and the differentiation between apparent and absolute increase are complex problems. The issues are particularly involved in bronchogenic carcinoma because pathological recognition preceded clinical detection by many decades with each era reflected in increased incidence. During the 19th century, primary cancer of the lung was essentially a necropsy finding. Clinical investigation was limited to the physical examination and the cytological study of the sputum. This assured a high degree of accuracy but, at the same time, limited the number of diagnosed cases.

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The establishment of pathology as a medical discipline resulted in greater interest in the post-mortem examination and more meticulous microscopy. By the end of the century the European literature was replete with dissertations, theses and case reports on the "rare disease". Awareness of lung cancer had also occurred in this country and the number of publications prior to 1900 was not inconsiderable. Adler, in a comprehensive monograph published in 1912, stated unequivocably that the increased necropsy incidence of lung cancer was the result of better pathological diagnosis. He also emphasized that the disease was difficult to diagnose clinically and questioned the validity of the national census statistics which, at that time, showed less than 400 lung cancer deaths annually for the entire United States.

In the years following World War I, a resurgence of interest in pulmonary cancer occurred sparked by the publication of numerous statistical studies from the large European municipal hospitals. On February 13, 1926, the Journal of the American Medical Association commented editorially that the number of cases reported in the preceding 15 year period was so great as almost to defy enumeration. However, the official statistics for lung cancer during that period showed less than 2000 annual deaths in the United States. The possible causes cited for the increase included cigarette smoking, air pollution and post-influenzal epithelial proliferation. The last etiological suggestion seemed most plausible and was supported by several pathologic studies in this country and

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abroad. On September 7, 1935 the Journal again editorialized on the increasing interest in bronchogenic carcinoma summarizing some of the later pathologic studies on histogenesis.

The differential diagnosis of thoracic diseases is a relatively recent development and there are many examples of increased incidence following pathological and clinical recognition. According to Foster-Carter, the total number of cases of bronchial adenoma in the literature prior to 1941 did not exceed a hundred. One decade later, McBurney reported a greater number from the Mayo clinic alone. Ecological influences such as inhalant carcinogens can scarcely be incriminated since (1) the tumor originates below the surface epithelium and (2) the clinical history prior to bronchoscopic biopsy is often of many years duration. Another classical illustration is furnished by mesothelioma of the pleura which was considered among the rarest of tumors and its very existence questioned. The recent routine utilization of exploratory thoracotomy, pleural biopsy and cytological examination of pleural fluid has resulted in a steady increase in the number of diagnosed cases. There were almost 50 articles on mesothelioma cited in the 1962 edition of the Quarterly Index.

During the past three decades, the wave of interest in lung cancer assumed tidal proportions because of the large number of reported cases and the publicizing of statistical data correlating the disease with smoking. It is to be

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noted, however, that the increase occurred far more dramatically in clinically certified cases than it did at necropsy. In England, Willis observed that over a period of 20 years the rise in lung cancer necropsies had been very moderate in contrast to the tenfold increase in lung cancer death certificates.

A retrospective approach is required to properly interpret the rise in lung cancer incidence. During the past 150 years a vast literature has accumulated which enables us to compare over a period of many decades (1) the prevalence of carcinoma of the lung, (2) the relationship between lung cancer and total cancer, (3) the trend in the rate of increase, (4) the sex and age predilection, and (5) the progress in establishing investigative facilities for clinical diagnosis.

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Lung Cancer in the 19th Century

The first comprehensive discourse on the pathology of lung cancer was written by Laënnec in the Dictionnaire des Sciences Médicales in 1815 under the picturesque title, "Encephaloides". The name was derived from the external appearance of the tumor which grossly resembled brain tissue. The descriptive findings established lung cancer as a specific entity and differentiated it from tuberculosis and other pulmonary diseases. There were earlier references to the subject in the writings of Morgagni, Baillie, Hey, Abernathy, Burns, and Bayle but these were incidental and chiefly of historical interest.

In 1819, the publication of De L'Auscultation Mediate, Laënnec's classic treatise on physical diagnosis, evoked considerable interest in both the disease and the possibility of clinical identification utilizing the new instrument, the stethoscope. The translation of the book by Forbes in 1821, provided English physicians with the opportunity for familiarizing themselves with the condition. They quickly adapted the term "encephaloid" but were somewhat piqued by Laënnec's complete disregard of the studies on lung cancer which had previously appeared in the English literature. Forbes expressed his indignation in unequivocal language in the preface to his translation while his more reserved colleagues confined their comments to snide aspersions on the value of the stethoscope.

De L'Auscultation Mediate received wide recognition and the fourth edition, in 1837, published posthumously, was greatly expanded and contained almost as much discussion on lung cancer in editorial footnotes as Laënnec had provided in the original

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provocative text. During this era, awareness of the disease by French physicians was manifested by many articles and case reports. Interest had also extended to clinical problems and as early as 1821 Andral had written a thesis on examination of the sputum in pulmonary diseases in which he suggested that the diagnosis of lung cancer could be established by the demonstration of fragments of "encephaloid" or "scirrhous" tissue. Bouillaud's article in 1826 not only stressed the primary nature of the growth but also speculated on the etiological role of previous inflammatory disease. In 1830, Begin, the Dictionnaire de Médecine et de Chirurgie Pratiques, discussed pathology, symptomatology, physical diagnosis, and the futility of specific medical or surgical therapy. Heyfelder's presentation on lung cancer in 1837 disseminated further clinical interest in the subject and won the author an award from the Medical Society of Toulouse. Within a few years the pathological entity, "encephaloid" had emerged into the clinical disease, "cancer de poumon" and the 1839 edition of Bayle's Traite des Maladies Cancereuses readily acknowledged the specificity of lung cancer as a primary malignancy.

Interest in pulmonary diseases has been evident in British medicine since the early 19th century. One of the most notable contributors to knowledge of lung cancer was William Stokes whose writings reveal a deep understanding of both the pathological and clinical features of the disease. In Diseases of the Chest, published in 1837, the chapter on "Cancer of the Lung" reflects considerable experience in the varied manifestations. Stokes noted that there were no pathognomonic characteristics

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of lung cancer; that the physical signs elicited were dependent on the anatomical site of the growth; and that inflammatory complications such as pneumonia or pleurisy obscured the underlying malignancy. Little has been added to his description of the symptons and sequelae of bronchial obstruction. Stokes' lectures and articles were widely quoted and he played an important part in stimulating interest in lung cancer among his contemporaries.

In 1838, an article by Hare appeared in the London Medical Gazette which was entitled to more acclaim than history has awarded it. By means of a well documented case report there is described the clinical picture which results when cancer of the lung invades the cervical sympathetic ganglia and brachial plexus. The patient exhibited all the stigmata which are now classified as Horner's syndrome and in addition had complained of pain and swelling in the ipsilateral arm. The report is of particular historical interest because of the rediscovery of these clinical features in 1932, almost a century later, under the title of "superior pulmonary sulcus tumor".

In April 1843, the British and Foreign Medical Review considered the subject of cancer of the lung of sufficient importance to review five recently published articles. The opening remarks of the review were, "Did space permit, we should almost be tempted by the present favorable opportunity to enter into a complete examination of cancer of the lung in its anatomical, pathological and practical relations. We should be justified in this course by the increasing interest in the subject and above all by the obvious fact that while as a pul-

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monary affection productive of symptoms, is much greater than had until of very late years been suspected, it may at the bedside be confounded with diseases from which it is all important to distinguish it." The articles included "Inauguralis des Cancreaux Pulmonom" by Van Kleffins, "Cases of Malignant Disease of the Lung" by Hughes, "Clinical Lecture on Cancer of the Lung" by Taylor, "Researches on the Pathology and Diagnosis of Cancer of the Lung and Mediastinum" by Stokes, and "The Physical Diagnosis of Diseases of the Lungs" by Walshe. The critique concluded with the wry observation that the authors showed laudable discretion in omitting references to treatment.

The article by Hughes which appeared in Guy's Hospital Reports in 1841 was an excellent example of integrity in medical reporting. The author noted that, despite the pathological recognition of lung cancer at Guy's Hospital for more than a decade, the diagnosis had rarely been established until the post-mortem examination. Many of the cases had no pulmonary symptoms such as cough, dyspnoea, or pain and, in some instances, thoracic disease was not even suspected. Hughes predicted that increasing interest in the problem would eventually result in more precise utilization of auscultation and percussion. One of his significant observations repeatedly confirmed in later decades, was that the disease had a tendency to metastasize and that the clinical manifestations produced by the metastases often dominated the course of illness.

The extent of progress in knowledge of cancer of the lung was aptly summarized in an article by MacLachlan in 1842 in the

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London Medical Gazette. Within a period of two decades the disease had been differentiated from inflammatory conditions and from other malignant lesions involving the lung. Familiarity with the pathologic pattern in the lung and the extent of the metastatic foci was evidenced in the more frequent use of the title "Primary Cancer of the Lung" in case reports. Equally significant was the realization that the disease could occur without typical symptoms and signs and that clinical recognition was confronted with many difficulties inherent in the nature of the tumor.

The now familiar syndrome produced by compression of the superior vena cava by metastatic involvement of mediastinal lymph nodes was described in 1844 by Burrows in the Medico-Chirurgical Transactions and by O'Ferrall in the Dublin Medical Journal. Their vivid delineation of the edematous patient with distended superficial veins and dysphagia added further understanding of the manifestations produced by regional extension of the tumor. Another contributor to clinical knowledge during this era was Graves, who emphasized the obscurity of the initial symptoms in his textbook, Clinical Lectures on the Practice of Medicine. A very pointed remark was made in the Dublin Journal of Medical Science in 1843, as a post-script to a case report of "lardaceous schirrhoma of the lung". The clinical and pathological manifestations of the case had been characteristic of primary cancer of the lung and the editorial comment was, "had the author been aware of the point of diagnosis established by Dr. Stokes (on cancer of the lung), he could hardly have mistaken the nature of the disease".

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The interest created in lung cancer in France by Laennec and his contemporaries was perpetuated by contributions from Bleu in the Bulletins de la Société Anatomique in 1846; Arnal, in the Gazette des Hôpitaux in 1844; Bérard in 1828 in the Bulletins de las Société Anatomique; Lebert, in Physiologie Pathologique in 1845; and many others. The description of "cancer des poumons" by Monneret and Fleury, in 1846, in the Compendium de Medicine Pratique included an excellent discussion of pathology, anatomy, symptoms, signs, differential diagnosis and, in addition, a bibliography of considerable proportions.

In the second half of the 19th century a new dimension was added to the study of lung cancer. The concept of cellular pathology introduced by Virchow and Rokitansky in Germany, began to be applied everywhere to the histologic study of tumors. Gross descriptions of the pulmonary lesions were no longer considered adequate and microscopic examinations became part of the post-mortem routine. Tumor differentiation was correlated with histologic structure to provide more accurate pathologic diagnoses. As early as 1857, case reports in England by Quain, Cockle, Mayne, and Pitman showed an awareness of the significance of microscopic findings. In one of the cases reported by Quain in the Transactions of the Pathological Society of London there is an excellent description of the mucosal spread of malignant cells into the "air vesicles". The tendency for malignant thrombi to form in the pulmonary veins rather than in the arteries was noted by several authors. Quain stated "while the venous system was thus prone to assume the disease, the arterial appeared to enjoy a complete immunity....." Pitman, writing in

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the British Medical Journal for October 31, 1857 also commented that the arteries "seemed quite exempt from the disease", an observation which has been confirmed many times over.

As the era of the complete necropsy examination became more firmly established the pathologic protocols transcended the mere objective of tumor diagnosis. This was very apparent in the report by Lanceraux in the Bulletins de la Société Anatomique, in 1858, wherein the author not only described the lesion in the lung but also gave a detailed account of the metastatic deposits in the other organs. The routine examination of all other viscera to exclude the possibility of primary tumor elsewhere was an important contribution. In a case report in the Medico-Chirurgical Transactions in 1859, Budd concluded the article with the simple but decisive statement, "there is no other cancer in any other part of the body". Studies of a similar nature were also contributed by Begbie in 1860, in the Archives of Medicine, Descroizilles, in 1861, in the Gazette Hebdomadaire and by page, in 1862, in the Lancet. It was interesting to note in the literature of this period that the case reports of lung cancer were being presented at hospital conferences and staff meetings with increasing emphasis on complete post-mortem findings.

In 1861, the comprehensive monograph, "Du Cancer du Poumon" by Aviolat was published in France. The 95 page discourse reviewed the story of lung cancer in preceding decades in terms of history, symptoms, signs, and pathology and furnished an excellent bibliography. A similar dissertation, of lesser magnitude was contributed by Botesato, in Berlin, 1863 under the

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title, "De Carcinomate Pulmonum et Pleurae". An early clue to the bronchogenic origin of lung cancer was furnished by Beveridge in 1869 in the Medical Press and Ciruular. The case was one of sudden death in which the diagnosis of lung cancer was established after necropsy. Pathological examination had demonstrated a mass in the bronchial lumen with extension into the lung parenchyma. The significance of this finding was not fully appreciated for another decade.

Many reports at the time disclosed awareness of the presence of bronchial obstruction on the basis of physical signs and necropsy findings but considered the bronchial compression of extrinsic origin. In a case report by Powell, in 1868, the pulmonary tumor is well described but origin is attributed to the adjacent mediastinal glands. Salter, in a lecture in 1869, displayed accurate knowledge of the physiologic changes resulting from bronchial obstruction but visualized the tumor as encroaching on the bronchus and encircling it. Beale, in 1869, described detailed necropsy findings in a case report in the Medical Times and Gazette but was confused about the direction of spread and attributed the site of origin to the mediastinal glands. The error was perpetuated for many years and Davy, reporting a case in the Lancet in 1882, stated that the origin of the carcinoma was at the root of the lung and that the tumor had subsequently surrounded a large bronchus to obstruct it. He was surprised that the growth had been in only one direction and that the contralateral lung was entirely uninvolved. The inability to perceive the bronchogenic origin of lung cancer for so many years was due to the nature of the material available for study

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which usually represented far advanced disease with excessive Pulmonary and mediastinal involvement.

In 1872, James Bennett published the book, "Intrathoracic Growths" which contained the substance of the Lumleian lectures previously appearing in the British Medical Journal. Bennett referred to 39 cases of lung cancer in his personal experience and presented the material in a scholarly manner. Although primarily a clinician, his interest in pathology led him to differentiate between lymphosarcoma involving the mediastinum and lung cancer with mediastinal metastases. Bennett's lectures received wide recognition and he contributed a great deal to the dissemination of knowledge on pulmonary neoplasms. During this period many cases of lung cancer were published in the Transactions of the Pathological Society of London. In a report by Leared, in 1870, there is mentioned the existence of a committee on morbid growths which apparently had to certify each case before publication. The author's microscopic description of "cellular formations intermingled with fibrous substance" has been repeated many times since by pathologists in all languages. Smith-Shand, in 1875, commented in the British Medical Journal that despite all the writing on lung cancer, the disease still frequently baffled the diagnostic skill of the physician. The author's vivid description of the clinical manifestations was well correlated with the necropsy findings of "an encephaloid mass plugging the bronchus" and extending to the lung and mediastinal structures.

Although cancer of the lung continued to be predominantly a necropsy diagnosis for many more decades, it was evident in the English literature that clinical interest had become well

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established. In 1871, Reynold's System of Medicine contained a comprehensive article on cancer of the lungs by Herman Biegel. The subject was presented in the customary formal textbook manner with subdivisions on symptoms, physical signs, pathological anatomy, and complications. A bibliography was also included. The author was well aware of the problems of differential diagnosis, particularly, the exclusion of metastatic cancer from other primary sites. In the same year, Walshe, in Practical Treatise on Diseases of the Lungs noted that cancer of the lung was "very much less rare than was till recently supposed" and listed the varied physical signs in "tabular arrangement" to differentiate lung cancer from pulmonary cirrhosis, chronic pneumonia, tuberculosis, and chronic pleurisy. He noted, in a collected series of 136 cases, that cancer of the lung was more prominent in the male and that most cases occurred in the 5th decade.

By 1875, the status of cancer of the lung as a significant pulmonary disease was well established in England, France, and Germany. In the United States, there were a few cases reported prior to this era but interest in pathology had lagged considerably behind that of the European countries and little was apparently known of the disease. In 1850, in the New York Journal of Medicine, there appeared a rather comprehensive article by MacDonnell who was on the staff of McGill College. The doctor was very familiar with the pathology and clinical course of lung cancer and his report equalled in thoroughness any of the contemporary studies published abroad. In addition to an excellent exposition of physical signs, there was a re-

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view of the extra-thoracic manifestations resulting from involvement of the cervical sympathetic nodes, brachial plexus, and superior vena cava. Storer, in 1851, described a case from the Massachusetts General Hospital and emphasized that diagnostic clinical features had occurred very late in the course of the disease. A case report by Lehlbach, in 1870, in the Transactions of the Medical Society of New Jersey, was of unusual interest, historically, because microscopic examination of the sputum was mentioned, casually, as if it had been a routine procedure. Francis Delafield, at the time pathologist at Roosevelt Hospital, New York City, kept a special notebook with the title, "Case Reports of Tumours of the Lung, 1868-1888", in which were recorded in his own handwriting, protocols of cases of primary cancer of the lung. In 1876, Loomis discussed lung cancer in Lectures on Diseases of the Respiratory Organs, Heart and Kidneys and tried to differentiate between primary and secondary lesions.

The extent of accumulated knowledge on lung cancer was also very evident in France and Germany in the early 1870's. Jaccoud, who had previously made many case reports in various journals, contributed an excellent article in 1872 in the Traite de Pathologie Interne. An intensive clinical discussion appeared in 1873 in the doctoral thesis, "Du Cancer Pulmonaire", by Camo-Abdon. In a disseration at Wurzburg, in 1874, Schottelius gave an excellent description of lymphangitic spread throughout the lung from the primary lesion. Ziessman's Cyclopedia of Practice of Medicine, in 1875, had a chapter on pulmonary neoplasms by Hertz. Lataste, in 1875 reported an interesting case in the Bulletins de la Société Anatomique with a detailed histo-

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logic discussion of malignant epithelial changes. In 1872 an extensive statistical study was made by Eppinger at the Prague Pathological Institute which showed a significant necropsy incidence of carcinoma of the lung. The study was reported in the Vierteljahrschrift Für Die Praktische Heilkunde.

During the last quarter of the 19th century the literature began to include an increasing number of histological studies. In the early 1870's, Waldeyer had written a series of articles on the origin of carcinoma from epithelial tissue which paved the way for establishing the histogenesis of lung cancer from the columnar cells of the bronchial mucosa. Perls, in 1872, indicated in his report in the Archiv Für Pathologische Anatomie that he was familiar with the previous studies and demonstrated mucosal origin of the tumor from a bronchial lumen. Malassez's article, in 1876, in the Archives de Physiologie has since become a medical classic. His studies demonstrated epithelial proliferation and extension into the parenchyma with the formation of gland-like structures by the malignant epithelial cells lining the alveolar spaces. The term alveolar carcinoma, has subsequently come into general use with varied connotations of specifity. Malassez, however, believed that the origin of the epithelial cells lining the alveoli was from the terminal bronchioles. Another histologic contribution was the description of lymphatic extension from the tumor to the mediastinal glands and along the superficial lymphatics of the pleura. Contemporaneous with Malassez's studies, a series of articles on metaplasia by Friedlander was published in Germany. The similarities between post-inflammatory epithelial prolifera-

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ation and malignant metaplasia were noted and a possible etiologic relationship was suggested.

Although Virchow made no direct contribution to the study of lung cancer, his authoritative works influenced all pathological examinations and led to more meticulous necropsies. This was very evident in the German case reports in the latter part of the 19th century. An article by Georgi, from Kussmal's clinic, published in the Berliner Klinische Wochenschrift in 1879, exemplified very careful study. The tumor in the particular case was limited to the lung and the author demonstrated that the site of origin was the epithelial surface of the bronchial wall. Reinhardt, in 1878, contributed an excellent discussion in the Archiv für Heilkunde emphasizing the increased incidence of the disease in his time. In the succeeding years greater significance of Waldeyer's studies on the epithelial origin of carcinoma was reflected in the increasing usage of the term "primary cancer of the bronchus". Stilling, in 1881, in the Archiv für Pathologische Anatomie, included in his presentation illustrative sketches depicting pulmonary cancer arising from the epithelial mucosa of the tertiary bronchi.

In both the German and French literature the areas of pathological confusion were gradually being clarified. Birch-Hirschfeld, in 1882, summarized the status of lung cancer knowledge in the Lehrbuch der Pathologische Anatomie. He clearly stated that primary carcinoma of the lung was an outgrowth from the epithelial mucosa of the bronchi and that it spread through the lymphatic channels and along the mucosal surface into the lumen of the alveoli. This concept was further

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emphasized by Ebstein, in 1890, in the Deutsche Medicinische Wochenschrift when he used the terms, cancer of the bronchus, and, primary cancer of the lung, interchangeably. He also commented on the necessity for pathological differentiation between lymphosarcoma and carcinoma because of the similarity in the clinical manifestations. An interesting article by See, in 1885, in Medecine Clinique des Maladies Specifiques (non Tuberculeuses) du Poumon discussed problems in clinical diagnosis when the presenting symptoms were due to pleural or mediastinal invasion. Diversity of metastases from primary lung cancer was stressed by Jaccoud, in 1873, in the Traite de Patholgie Interne. Menetrier, as an "intern des hôpitaux" contributed many interesting case reports in the Bulletins et Memoirs de la Société Anatomique. Muselier, in 1886, in the Gazette Medicale demonstrated that the disease often began insidiously and that there was little correlation between the anatomic extent of the disease and the symptoms. He described a case in which the predominant manifestation was paraplegia due to metastases to the vertebral column.

In 1883, in the St. Bartholomew's Hospital Reports, Kidd made an important observation which has since proven of value in differentiating primary from metastatic cancer of the lung. He noted that despite the extensive encroachment of the primary tumor within the lung, the structural integrity of the organ with respect to alveolar pattern remained preserved. During this decade, the Transactions of the Pathological Society of London published many reports of primary carcinoma of the lung. Hanford reported 4 cases, 3 within the 12 months period ending June 1888. In one of his articles he stated that he saw 2

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other cases but did not wish to report them because there was no necropsy confirmation. Boyd reported 3 cases of lung cancer in the Lancet in 1887 with gross and microscopic descriptions and emphasized that "Primary cancer of the thorax is not of infrequent occurrence, ... it is a subject, the importance of which cannot be exaggerated, and the difficulties in the diagnosis of which, all physicians must admit."

Progress in pathology and increased familiarity with the European literature were reflected in the United States in greater interest in lung cancer during the latter decades of the 19th century. An article by Pepper, in 1878, in the Philadelphia Medical Times had the title, "Two Clinical Lectures on Primary Intrathoracic Carcinoma". The author was well acquainted with the Lumleian lectures previously published in the British Medical Journal and helped to perpetuate both the facts and the fancies. Van Giesen reported a case of "sarcoma of the lung" in the New York Medical Journal in 1879 but the description of the clinical features and necropsy findings suggested that the tumor had been a carcinoma. (The histological confusion between sarcoma and undifferentiated carcinoma existed for a long time and was not resolved until Barnard's studies in 1926.) In 1880, Ripley presented an excellent report in the Medical Record. His lucid demonstration of the histologic origin of the tumor and its dissemination by way of lymphatic channels was of sufficient interest to inspire an editorial on lung cancer in the same journal a few weeks later. On December 18, 1880, the Medical Record called attention to studies in Germany and commented that pathological interest in pulmonary cancer will

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continue to exist despite the inability to do more than palliative treatment.

Kemper, in 1882, reported an instance of primary cancer of the lung in the Transactions of the Indiana State Medical Society. The article referred to cases in the English literature and to those previously published in the United States. On February 24, 1883, Janeway described a case in the Medical Record and commented on 3 other cases he had treated. In 1889, Hare wrote a textbook, Pathology, Clinical History and Diagnosis of Affections of Mediastinum, in which considerable attention was directed to carcinoma of the lung and 134 collected cases were listed with individual data. Hodenpyl, in 1895, reported a case in the Proceedings of the New York Pathological Society in which the symptoms were precipitated by injury to the chest wall. The histologic features were indicative of undifferentiated carcinoma but the diagnosis, as in similarly described cases, was sarcoma.

The most informative American article of this era was contributed by Adler in the New York Medical Journal, February 8, 1896. The author stated that despite the extensive literature that had accumulated on lung cancer, the current textbooks had treated the subject in a cursory manner and that too many physicians were unaware of the prevalence of the disease and of its clinical manifestations. Adler decried the general lack of detailed microscopy in post-mortem examinations and urged a constant effort toward better differentiation of malignant growths. The histogenesis of bronchogenic carcinoma was clearly described and he emphasized that the tumor originated from the

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cylindrical epithelium of the bronchial mucosa. He accepted the existence of an alveolar epithelial lining which could give rise to alveolar cell carcinoma.

If some adequate portion of Adler's article, in 1896, had been publicized or, reprinted in the American textbooks of the early 20th century, the statistical incidence of lung cancer in the United States would have increased many decades earlier. Adler was an ardent enthusiast of the subject and had a strong conviction that improved diagnostic techniques would result in the recognition of more cases. He suggested wider utilization of the sputum examination and aspiration biopsy. The coexistence of pulmonary tuberculosis and cancer was discussed with full appreciation of the difficulties of clinical differentiation.

In the last decade of the 19th century it was evident from the literature that the gap between European and American knowledge of lung cancer was beginning to close. Loomis, in 1895, reported a case in the Medical Record in which was emphasized the anatomical site of origin from the left lower bronchus and the subsequent mucosal extension filling the alveolar structures with sheets of malignant cells. In 1899, a case of combined tuberculosis and carcinoma of the lung was reported in the Charlotte Medical Journal. During the same year, LeCount wrote an article in the Transactions of the Chicago Pathological Society with a most detailed histologic discussion. He noted that complete destruction of the bronchus could occur making it impossible to trace the site of origin of the tumor. LeCount observed islands of malignant cells separated by banks of connective tissue resembling alveolar walls and recognized that

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the architectural structure of the lung had been preserved despite the extent of the growth. There was also an appreciation of the difference between inflammatory and malignant epithelial proliferation and a discussion of the variations in size and shape of the malignant cells.

Interest in lung cancer was further increased during the last years of the 19th century. Harris, in 1892, made a comparative study of the incidence of intrathoracic tumor in the City of London Hospital and in St. Bartholomew's Hospital for the preceding decade. The results were published in the St. Bartholomew's Hospital report with the conclusion that the disease was a fairly constant cause of hospitalization and formed a significant proportion of the annual necropsies. The author emphasized that diagnosis was difficult and, in cases of small tumors, practically impossible. The article concluded with an excellent differential diagnosis which revealed a humility created by extensive clinical experience. The transactions of the Pathological Society of London in almost every volume, contained reports of the disease with confirmation by the Committee on New Growths. Some of the case studies were most instructive, particularly, the one reported by Moore, in 1881, which described cerebral metastases from bronchogenic carcinoma confirmed by histologic examination. The implication that primary brain tumors may be simulated by metastases from the lung was an important contribution. The Transactions also contained case reports by Pitt, Handford, West, Smith, Bird and many others. Griffiths, in 1888, and Greenwood, in 1897, described cases in the British Medical Journal. Rowan, in 1898, in the Transactions of the Ophthal-

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mological Society of the United Kingdom, reported a case of metastatic carcinoma of the choroid from a primary tumor in the lung. A comprehensive article on lung cancer by Samuel West was published in the St. Bartholomew's Hospital Reports in 1897. West based his presentation on 61 cases and made pertinent observations on sex incidence and clinical manifestations.

Articles on lung cancer were equally abundant in France during this period. The Dictionnaire des Encyclopédie Science Médicales contained an extensive discussion by Barie in 1889. A noteworthy feature of Barie's article was the extended bibliography which contained approximately 200 references. It was interesting to observe that the French literature, similar to the contemporary English, was manifesting evidence of increasing accuracy in diagnosis. The former title "cancer du poumon" was gradually superceded by "cancer primitif du poumon" with the specific location of the tumor and the extent of the metastases. Spillman and Haushalter contributed a study on diagnostic considerations in the Gazette Hebdomadaire in 1891. There were also case reports by Auvard in 1882, in the Bulletins de la Société Anatomique, Leopold-Levi in the Archive Génerale de Médicale in 1895, and Hautecoeur, in 1886, in Le Progres Medicale. The Bulletins de la Société Anatomique contained numerous contributions on the subject among which were articles by Bouygues, in 1888, Boix in 1891, and Barnard and Vermarel in 1894. An article by Claisse, in 1899, with the title, "Diagnostic precoce du cancer du poumon par l'etude histologique des crachats" reflected the growing clinical interest in early diagnosis and fully recognized the possibilities of cytologic

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study of the sputum. Excellent discussions of lung cancer were contributed by Achard, in 1893, in the Manuel de Medicine and by Szelagouski, in 1900, in a thesis published in Paris. During the last decade of the century, the number of articles on lung cancer was most impressive, reflecting both clinical interest and prevalence of the disease.

The number of case studies and dissertations on "lungen-krebs" during this period exceeded the French and English contributions. This was a natural sequence of the German interest in pathology and, especially, the study of neoplasms. Hampeln, in 1887, in the St. Petersburger Medicinische Wochenschrift, demonstrated the clinical diagnosis of the disease from tissue fragments in the sputum. Frankel prescribed an excellent exposition of differential diagnosis in 1891, in the Deutsche Medicinische Wochenschrift and several case reports in the Berliner Klinische Wochenschrift in the following year. He also described an unusual case which has been often quoted in discussions of mesothelioma of the pleura. Siegert, in 1893, in the Archiv für Pathologische Anatomie contributed a detailed exposition on epithelial proliferation, metaplasia, distribution of site of origin, and alveolar carcinoma. In the same journal, Betschart, in 1895, elaborated further on diagnosis by sputum examination and Passler, in 1896, discussed lung cancer with respect to statistical considerations. In an article by Wolf, in the Fortschritte der Medicin, in 1895, the histologic patterns were further clarified and the classification of squamous carcinoma and adenocarcinoma was used to differentiate origin from bronchial mucosa or glands. Ernst, in 1896, in the Beitrage

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zur Pathologischen Anatomie and zur Allgemeinen Pathologie, discussed the significance of keratinization in squamous epithelium. Simmonds, in 1898, contributed an excellent review of the histology of lung cancer in the Munchener Medicinische Wochenschrift. Problems in clinical diagnosis were analyzed, in 1899, by Hellendall, in the Zeitschrift fur Klinische Medicin and by Herrmann, in the Deutsche Archiv fur Klinische Medicin. Lenhartz in 1899, in the Handbuch der Praktischen Medizin, summarized the prevailing data, emphasized the bronchial origin of the tumor, differentiated pulmonary carcinoma from other "bösartigen neubildungen" in the lungs, and referred to 14 cases in his own experience.

There were a tremendous number of German inaugural dissertations, some approaching textbook proportions. The authors included Stumpf in 1891 (Giessen), Werner in 1891 (Freiburg), Japha in 1892 (Berlin), Passow in 1893 (Berlin), Lemkuhl in 1893 (Kiel), Hofmann in 1893 (Zurich), Hillenberg in 1893 (Kiel), Benkert in 1895 (Bad Kissingen), Hartmann in 1896 (Kiel), Degen in 1897 (Zurich), Peritz in 1897 (München), Rosenthal in 1898 (München), Kaminsky in 1898 (Greifswald), Wack in 1898 (Wurzburg), Kluber in 1898 (Erlangen), Elisberg in 1899 (Königsberg), Froelich in 1899 (Berlin), Schmidt in 1899 (Jana), Minssen in 1900 (Kiel) and many more published in the various university centers. The dissertations were comprehensive discussions covering most of the aspects of lung cancer with emphasis on some particular pathologic or clinical phase and included case presentations from the author's personal experience. In 1899, Aufrecht contributed an extensive article on carcinoma of the lung, in Nothnagel's textbook on

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special pathology, which was translated in the United States five years later. Within 5 years after Roentgen's discovery of the X-ray its possibilities in clinical diagnosis were realized and attempts were made to develop a technique for examination of the thorax. An article by Weinberger, in 1901, in the Zeitschrift fur Heilkunde, contained excellent illustrations of densities representing lobar atelectasis secondary to malignant bronchial obstruction. Accompanying the X-ray pictures were microphotographs of the tumor specimens proving that the diagnoses had been confirmed at autopsy. During the same period, Killian was experimenting with the bronchoscope as a diagnostic instrument for direct visualization of bronchogenic carcinoma and described his findings in the Berliner Klinische Wochenschrift in 1900.

The 19th century literature on lung cancer was dominated by German, French, and English contributions but there were also scattered reports from other European countries including Poland, Norway and Italy. As early as 1873, Marchiafana's article in the Rivista Clinica de Bologna revealed great familiarity with contemporary progress. The author discussed the histogenesis of primary lung cancer and recognized the bronchial epithelium as the site of origin. He also described malignant metaplasia of the "cellule cilindriche" and the histologic pattern of the primary lesion and the metastatic foci. In the latter years of the century, interest was directed toward diagnostic considerations and "carcinoma primitivo del polmone" took its place in the medical literature with "cancer de poumon" and "lungenkrebs". Among the articles of clinical interest were

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reports by Papinio, in 1893, in the Rivista Veneta de Scienze Mediche; by Foa, in 1894, in the Giornale della R. Accademie di Medicina di Torino; by Raccuglia, in 1896, in the Gazzetta Degli Ospedali; and by Simonelli, in 1899, in La Riforma Medica.

It is impossible to estimate the incidence of lung cancer in the 19th century or even the number of articles published on the subject. Research is limited by a lack of indices and a multiplicity of obscure titles. The bibliographies contain a great many references of which more than 300 were consulted to provide the data for this discussion. The numerous case reports, theses, and dissertations make it very apparent that cancer of the lung was recognized as a pathologic entity throughout most of the 19th century, that the difficulties of clinical diagnosis were well established, and that the disease was far more prevalent than was generally realized.

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Sex Distribution of Lung Cancer

Statistical studies have shown a remarkable consistency in the sex distribution of lung cancer. Predilection for the male was noted in the mid 19th century and became increasingly more apparent with progress in diagnostic accuracy. Reports in recent decades have further emphasized male predominance, and sex ratios of 7:1 or higher are not infrequent.

Similar patterns of sex distribution have been found in national mortality statistics. In the United States in 1930 there were 1818 lung cancer deaths in males and 1019 in females (1.8:1). In 1940 there were 6057 male and 2029 female lung cancer deaths (3:1). A decade later there were 14,922 male and 3391 female deaths (4.4:1). For 1960 the figures were 30,800 males and 5000 females 6.2:1). In Great Britain in 1960, the Register General reported 22,000 lung cancer deaths with a sex ratio of 6:1. Clemmensen, in 1947, postulated a correlation between diagnostic precision and widening of the sex ratio; this prediction has been confirmed. During the past few years there has been a negligible increase in female lung cancer deaths in the United States in contrast to the progressive rise among males.

The sexual affinity of lung cancer for the male has led to ecological speculation implicating cigarette smoking. On the basis of statistical studies correlating smoking with lung cancer it has been proposed that the disparity in sex distribution is the result of heavier smoking habits among men. The validity of this hypothesis may be tested by (1) ascertaining the sex distribution of the disease prior to the era of widespread

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cigarette smoking, and (2) by determining the effect of increased consumption of cigarettes by females on the sex ratio. Reports from the U.S. Department of Agriculture and the U.K. Tobacco Manufacturers' Standing Committee indicate that cigarette consumption per adult in both countries did not exceed 1 pack per week prior to 1920, and this period has been arbitrarily chosen as the beginning of the era of heavy cigarette smoking. Necropsy studies in the late 19th and early 20th centuries have made it possible to compare the current sex distribution of lung cancer with that prevalent in the years prior to heavy cigarette smoking.

It is apparent from TABLE I that lung cancer was predominantly a disease of males during an era in which cigarette smoking was virtually non-existent. Most of the studies show a sex ratio of at least 3:1, and some are comparable to ratios reported within the past decade. It is of considerable interest that as early as 1895, Wolf's cases of "primäre lungenkrebs" from the pathologic institute of the Dresden municipal hospitals showed a distribution of 6:1 favoring the male, and Passler, in 1896, found a ratio of 3:1 in a collected series of 68 cases. In Hare's Pathology, Clinical History and Diagnosis of Affections of the Mediastinum, published in 1889, the ratio was also 3:1 in a series of 122 cases. Harris, in 1892, made a combined study at St. Bartholomew's Hospital and at the City of London Hospital for Diseases of the Chest and found a ratio exceeding 3:1. Lenhartz, in Leipzig, reported a ratio of 13:1 in 1899, and Feilchenfeld in 1901, in Berlin a ratio of 10:1.

Predominance of lung cancer in the male was evident in

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TABLE I

SEX DISTRIBUTION OF LUNG CANCER
BEFORE ONSET OF HEAVY CIGARETTE SMOKING ERA

Author	Years	Place	Males	Females	Ratio
Hare, H.	1830-1880	Collected Series	90	33	3:1
Buday	1870-1888	Kolozsvár	9	1	9:1
Harris, V.	1882-1891	London	52	17	3:1
Passler, H.	1878-1894	Collected Series	50	18	3:1
Wolf, K.	1885-1894	Dresden	27	4	6:1
West, S.	1897	London	47	14	3:1
Lenhartz	1893-1899	Leipzig	13	1	13:1
Feilchenfeld,J.	1895-1900	Berlin	20	2	10:1
Riechelmann,W.	1895-1901	Berlin	21	6	3:1
Watsuji, S.	1904	Berlin	4	1	4:1
Redlich, W.	1900-1905	Berlin	26	5	5:1
Haberfeld,W.	1887-1906	Vienna	48	20	2.4:1
Karrenstein	1908	Berlin	24	8	3:1
Feldner, O.	1908	Gottingen	6	1	6:1
Seydel	1900-1909	Munich	16	4	4:1
Adler, I.	1842-1911	Collected Series	269	93	2.9:1
Dormanns, E.	1901-1911	Munich	7	1	7:1
Weller, C.	1878-1912	Collected Series	70	17	4:1
King, D.	1875-1914	Boston	36	9	4:1
Rau, W.	1909-1914	Dresden-Friedrichstadt	13	2	6.5:1
Briese	1898-1916	Chemitz	44	16	3:1
Lavrinovitch	1915	Petrograd	42	19	2:1
Jaffe, R.	1915-1918	Vienna	92	8	11:1
Passey, R.	1894-1918	Great Britain	579	182	3.2:1
Rau, W.	1914-1919	Dresden-Friedrichstadt	22	5	4.4:1
Eichengrun,W.	1902-1919	Cologne	32	5	6.4:1

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both the individual necropsy studies and in the collected series of cases. Adler's book in 1912 spanned more than seven decades and included cases from London, Prague, Berlin, Jena, Rome, Paris, Glasgow, St. Petersburg, Zurich, and even Brooklyn. Despite the variety of sources the overall picture of male predilection was similar to Reichelman's report in 1902 from the Friedrichshain Hospital in Berlin, Karrenstein's in 1908, from the University of Berlin, and Briese's report, in 1916, from the Pathologic-Hygienic Institute of Chemnitz. Weller, who was among the first American pathologists to become interested in bronchogenic carcinoms, reported, in 1913, a series of 87 collected cases which he had subjected to the most rigid criteria with respect to primary origin, and found a sex ratio of 4:1.

In some instances it was possible to follow the sex ratio of lung cancer through several periods in the same institutions. In 1925, Berblinger completed a necropsy study previously originated by Laeschka at the Pathologic Institute of Jena. Lung cancer predominated in the male for each lustrum beginning with 1910, and the ratio for the fifteen year period was 4:1. Peters found a ratio of 3:1 between 1905-1908 at the Moabit and Urban Hospitals of Berlin and a ratio of 5:1 between 1917-1922. At the Dresden and Friedrichstadt hospitals and nursing homes, Junghanns found a ratio of 4:1 in the period 1893-1897 and again in the period 1898-1902. Dormanns found a sex ratio of almost 7:1 at the University of Munich in 1901-1911 and again in 1922-1931. In Cologne, Eichengrun and Esser found a ratio of approximately 6:1 in the period 1902-1914 and a 9:1 ratio in 1914-1919.

One of the most significant studies was that of Passey and

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Holmes from a group of teaching hosoptals in England and Scotland covering a period of more than 30 years and including the eras before and after the onset of heavy cigarette smoking. They found a sex ratio of 3:1 for each of the periods 1894-1898, 1899-1903, and 1909-1913. Between 1914-1918 the ratio was 4:1, and between 1919-1923 it was again 3:1. The highest ratio was 4.5:1 which occurred in the period 1924-1928.

In TABLE II is shown the sex ratio in the years that followed the widespread consumption of cigarettes. Male predominance is again apparent, but there are wide fluctuations in the sex ratios reported by different authors during similar periods of observation. It has been suggested that high sex ratios are indicative of greater diagnostic accuracy, and in the Denmark study by Clemmensen and Busk this point is well validated. During the same period, 1936-1945, the sex ratio for 1,984 cases of lung cancer in Denmark was 2.4:1 while the ratio found in 139 cases at the Central Tuberculosis Station in Copenhagen was 7.2:1, and for patients over forty-five years of age it was 8:1. The authors were very explicit about the superior facilities for differential diagnoses at the Central Tuberculosis Station as contrasted with the average for the rest of the country. Confirmation that the high sex ratio was due to greater diagnostic accuracy was obtained by reviewing the mortality statistics which showed no increase in the incidence of lung cancer among males at the clinic from 1936-1945 while the corresponding mortality rate for Copenhagen, Frederiksberg and Gentofte had tripled.

It is generally acknowledged that selectivity may be a significant factor in necropsy statistics, but the unanimity of

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TABLE II

SEX DISTRIBUTION OF LUNG CANCER
AFTER ONSET OF HEAVY CIGARETTE SMOKING ERA

Author	Years	Place	Males	Females	Ratio
Berblinger, W.	1920-1924	Jena	34	8	4:1
Fishberg, M.	1914-1926	New York City	44	16	2.7:1
Shennan, T.	1914-1927	Aberdeen	18	4	4.5:1
Wahl, S.	1917-1927	Berlin	64	17	3.7:1
Schonherr, E.	1919-1927	Chemnitz	73	17	4.3:1
Maxwell, J.	1912-1928	London	83	17	4.9:1
Lipschitz, M.	1909-1928	Zwichau	83	6	14:1
Passey, R.	1919-1928	Great Britain	743	195	3.8:1
Kuhn, C.	1900-1929	Neukolln	151	27	5.6:1
Freemont-Smith,M.	1915-1929	Boston	17	1	17:1
Metzmacher, P.	1918-1929	Cologne	55	6	9:1
Schlesinger, M.	1924-1929	Dusseldorf and Leipzig	127	23	5.5:1
Funk, E.	1930	Philadelphia	50	11	4.5:1
Buschbeck, H.	1923-1930	Dresden	122	19	6.4:1
Abraham, M.	1908-1932	North Africa	22	5	4.4:1
Sitsen, A.	1926-1934	Innsbruck	19	3	6:1
Jaffe, R.	1929-1934	Chicago	92	8	11.5:1
Harvey, C.	1910-1935	New South Wales	87	13	6.7:1
Halpert, B.	1930-1940	New Orleans	123	12	10:1
King, A.	1942	Baltimore	114	18	6.3:1
Fried, B.	1914-1944	New York City	250	69	3.7:1
Clemmesen, J.	1936-1945	Copenhagen	122	17	7.2:1
Rosenblatt, M.	1920-1949	New York City	183	25	7.3:1
Ibrahim, M.	1951-1953	East Pakistan	18	2	9:1
Sabour, M.	1952-1960	Cairo and Grimsby	458	51	9:1
Farago, C.	1958-1962	New Guinea	23	6	4:1

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reports on lung cancer sex ratios from so many different localties tends to preclude this. It is possible, however, that factors pertaining to diagnostic experience, autopsy percentage and sex and age distribution of hospital populations may explain the variations in sex ratio among the various hospitals. Jaffe and Sternberg, in a necropsy study from military hospitals in Vienna, 1915-1918, found 92 lung cancers in males and 8 in females (11.5:1). In 1935, Jaffé reported the identical sex incidence from the Cook County Hospital in Chicago suggesting that the high sex ratios were more related to the natural predilection of the disease and the author's experience than to the composition of the hospital population or to the degree of cigarette consumption.

In some instances selectivity may affect the sex ratio considerably. MacFarlane, Doughty and Crosbie attributed a sex ratio of 13.5:1 at the London Chest Hospital in 1960 to the greater interest of male lung cancer patients in surgical therapy. This correlation was also observed in the United Birmingham Hospitals by Taylor in 1950-1954 when the sex ratios for all lung cancer admissions was 8.6:1 and the ratio for surgical cases was 12.4:1. Among the lowest sex ratios found in recent years was 4:1, reported by Farago from Papua and New Guinea where diagnostic facilities and life expectancy are limited and cigarette smoking is widespread.

The studies show unequivocably that male predominance in lung cancer is an inherent characteristic of the disease, that it had also occurred before the onset of heavy cigarette smoking, and that the increase in the sex ratio is, in all probability, a reflection or greater diagnostic accuracy. It is also apparent that

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predilection for the male occurred in all localities where lung cancer was found and among all races. It is of interest that Ibrahim in 1954 reported a sex ratio of 9.1 in East Pakistan where cigarette smoking is a rarity.

Sex Distribution and Smoking

There has been a progressive increase in cigarette consumption by women for more than four decades. A survey of smoking patterns by the U.S. Bureau of the Census in 1955 stated that 18,000,000 women, 18 years of age and over, had reported use of tobacco, and that 15,000,000 had at one time or another been regular cigarette smokers. The corresponding figures for men were 38,000,000 and 31,000,000, respectively. The survey acknowledged that it had underestimated cigarette consumption by 15 per cent on the basis of comparable tax data, and common observation suggests even a greater margin of error.

According to the various prespective and retrospective studies cigarette smoking is alleged to be a potent carcinogenic agent. It is difficult to reconcile this conclusion with the continued predominance of the disease in men despite the prodigious rise in cigarette consumption by women. During all the years of increased female smoking there has not been the slightest narrowing of the sex ratio indicative of a relative increase of lung cancer among women. It has already been emphasized that the sex ratio has actually widened. Inasmuch as diagnostic facilities are equally available to both sexes, it is more logical to assume that the continued increase in men is the result of sex predilection of the disease rather than of smoking.

Data from the U.S. National Office of Vital Statistics show

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that lung cancer death rate between 1930 and 1958 increased twelve times for men and three times for women. The greatest increase among women occurred between 1930 and 1950 during which time the rate rose from 1.5 per 100,000 to 4.0 per 100,000. Since 1950 the rate showed little increase. The sex ratio with respect to mortality rates was 1.7:1 in 1930 and 6.6:1 in 1958 emphasizing the relative decrease among women during an era of heavy cigarette smoking. Mortality statistics in succeeding years show no indication of changing trends. The total increase of male lung cancer deaths between 1959 and 1962 was 4,665 .* The increase of female lung cancer deaths for the 4 year period was 333 cases.

It is evident from the foregoing that the tremendous increase in cigarette smoking by women did not result in any comparable rise in lung cancer deaths or in reduction of the sex ratio of the disease. During the past few years the female lung cancer death rate has remained virtually stationary. It is scientifically incongruous to attribute the etiology of lung cancer to cigarettes when 15,000,000 regular women smokers show an annual increase of less than 85 cases. The rapid adoption of the smoking habit by women over a short span of years would have resulted in a continuing epidemic of lung cancer if tobacco were the causative agent.

Age Distribution of Lung Cancer

Observations for considerably more than a century have shown that lung cancer is primarily a disease of older age groups with most cases occurring in the 5th, 6th, and 7th decades. Simons, in a collected series of more than 5,000 cases found that 80 per cent

* Mortality statistics for 1962 estimated by American Cancer Society.

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had occurred between 40 and 70 years of age. Lung cancer is uncommon below the age of 40 and rare during the first three decades of life. It is seen, in TABLE III that the predilection for older age groups was noted consistently in all the statistical reports before and after the onset of heavy cigarette smoking.

The age distribution of lung cancer has a definite relevancy to the etiological considerations. It has been alleged that cigarette smoking produces a cumulative carcinogenic effect over a period of approximately two decades. If this concept is valid, the segment of the cigarette smoking population which began smoking in the early teen ages should develop lung cancer before 40 years of age. No indication of this has occurred in over forty years of heavy cigarette smoking. Data from the World Health Organization show a uniform curve of age distribution in the United States, the United Kingdom, Germany, and Italy with the greatest number of cases between 55 and 64 years of age and only a small proportion before 44 years of age.

The age at which the lung cancer patient started to smoke has no relation to the age in which the disease was acquired. Patients who began smoking in the early teen ages and those who began 20 or more years later developed lung cancer during the same later period of life, namely, in the 5th, 6th, or 7th decade. Furthermore, there is no evidence that the lung cancer patient who was a heavy smoker developed the disease at an earlier period of life than the patient who was a light smoker. If tobacco is a potent carcinogen the amount consumed and the duration of smoking should have some relationship to the onset of the disease.

Passey studied the smoking histories of 495 men with lung

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TABLE III

AGE DISTRIBUTION OF LUNG CANCER

BEFORE ONSET OF HEAVY CIGARETTE SMOKING							AFTER ONSET OF HEAVY CIGARETTE SMOKING						
Author	Year	*Decade 4th	5th	6th	7th	8th	Author	Year	*Decade 4th	5th	6th	7th	8th
Walshe, W.	1846		+	+			Frenczy, K.	1915		+	+	+	
Reinhard, W.	1876		+	+	+		Seyfarth, C.	1924		+	+	+	
Hare, H.	1880	+	+	+			Hanf, O.	1925			+	+	+
Buday	1888		+	+	+		Fishberg, M.	1926		+	+	+	
Harris, V.	1891	+	+	+			Shennan, T.	1927		+	+		
Passler, H.	1894		+	+	+		Schonherr, E.	1927		+	+	+	
Wolf, K.	1894			+	+		Wahl, S.	1927			+	+	
West, S.	1897		+	+	+		Maxwell, J.	1928		+	+		
Lenhartz	1899			+	+		Kuhn, C.	1929		+	+	+	
Feilchenfeld, J.	1900		+	+	+		Freemont-Smith, M.	1929	+	+	+		
Riechelmann, W.	1901	+	+	+	+		Schlesinger, M.	1929			+	+	+
Sehrt, E.	1903		+	+	+		Funk, E.	1930	+	+	+		
Watsuji, S.	1904		+	+	+		Buschbeck, H.	1930		+	+	+	+
Redlich, W.	1905		+	+	+		Sitsen, A.	1931		+	+	+	
Haberfeld, W.	1906		+	+	+		Jaffe, R.	1934		+	+	+	
Karrenstein	1908		+	+	+		Harvey, C.	1935		+	+	+	
Seydel	1909		+	+	+		Halpert, B.	1940		+	+	+	
Adler, I.	1911		+	+	+		King, A.	1942		+	+	+	
Dormanns, E.	1911		+	+	+		Fried, B.	1944			+	+	
Weller, C.	1912			+	+		Rosenblatt, M.	1949		+	+	+	
King, D.	1914		+	+	+		Ibrahim, M.	1953		+	+	+	
Rau, W.	1914		+	+	+		Sabour, M.	1960		+	+	+	
Briese	1916		+	+	+		MacFarlane, J.	1960		+	+	+	

* Decades in which majority of cases occurred

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cancer and found that they had acquired the disease at approximately the same age regardless of whether smoking had been started at 6 years or at 41 years of age. It was also revealed that the number of cigarettes consumed daily did not influence the age of onset of disease; the light smoker was affected with lung cancer at the same age as the heavy smoker. Passey concluded that lung cancer was more related to the age of the individual than to the extent of cigarette smoking.

Rate of Increase of Lung Cancer

Comparative studies of the annual deaths from lung cancer provide data to interpret the trend in incidence. General awareness of lung cancer did not exist in the United States until the third decade of the 20th century. During a period when the German literature contained necropsy reports involving, literally, thousands of cases many American institutions were just beginning to recognize the disease. Symmers found only 34 cases at Bellevue Hospital prior to 1925 out of a total of over 13,000 autopsies; at the Memorial Hospital for Cancer the annual incidence rate prior to 1930 averaged less than 10 cases; and in a combined study of northwestern hospitals, Menne and Anderson found but 3 cases between 1920 and 1925. Within a decade, all institutions were reporting increasing number of cases. A sufficient number of years have elapsed to determine whether the epidemic was the result of mass enlightenment or mass influx of new cases.

The earliest statistics for lung cancer in the United States showed 371 deaths in 1914, 956 deaths in 1920, 2,357 deaths in 1930, and 4,237 deaths in 1940. The total annual deaths continued

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to rise thereafter but the greatest increases occurred in those areas where the 1940 lung cancer death rate had been relatively low. Lew noted that between 1940 and 1950 the greatest rise in the death rate (347 per cent) had occurred in South Carolina where there were 74 physicians per 100,000 population and the smallest rise (55 per cent) was found in New York with 203 physicians per 100,000 population. It was very apparent from the study that the magnitude of the lung cancer death rates was dependent on medical awareness of the disease and facilities for diagnosis.

The incidence of lung cancer in the United States followed the same pattern that had occurred abroad in earlier years, namely, a rapid rise followed almost immediately by a progressive decline in the rate of increase. TABLE IV illustrates the variations in the rate of increase in the United States over a period of approximately 45 years. The greatest rate of increase in lung cancer occurred between 1914 and 1930 when criteria for pathologic recognition were being established. The studies on histogenesis by Barnard in England and Saphir in this country had clarified the problem of the "oat cell sarcoma" and a large group of tumors was included in the category of lung cancer. It is no coincidence that this was also a period when a great many hospitals in the United States acquired full time pathologists and the microscopic examination was added to the necropsy routine. Corroborative evidence of the large increase was furnished by the records of the Metropolitan Life Insurance Company which showed a 100 per cent rise in the standardized annual death rate from lung cancer between 1917 and 1926.

Since 1930 there has been a progressive decline in the rate

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TABLE IV

MORTALITY OF LUNG CANCER IN THE UNITED STATES

*Year	Number of Deaths	Per Cent Increase
1914	371	(No camparative data)
1920	956	158
1930	2,357	146
1935	4,237	79
1940	7,121	68
1945	10,922	53
1950	18,313	67
1955	26,827	46
1960	37,500	39

* Data for 1925 not available

TABLE V

MORTALITY OF LUNG CANCER IN NEW YORK STATE

*Year	Number of Deaths	Per cent Increase
1931	615	(No comparative data)
1935	1,006	64
1940	1,440	43
1945	2,041	42
1950	2,711	33
1955	3,779	39
1960	4,451	18

* Data for 1930 not available

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of increase. The lustrum, 1955-1960, shows an increase less than half that of 1930-1935. Although the total number of lung cancer deaths is still increasing the trend is definitely toward a lower rate and stabilization of the incidence of the disease.*Gilliam has emphasized that continued decline in the rate of increase eventually leads to a reduction in total incidence.

During the 25 years of the declining rate of increase of lung cancer the number of cigarette smokers continued to multiply. Latest available data show that cigarette consumption has increased more than 200 times since the turn of the century. It is exceedingly difficult to reconcile the tremendous rise in cigarette smoking with the progressive decline in the rate of increase of lung cancer if tobacco is a carcinogenic agent. The facts suggest rather that the sudden increase in incidence followed the acquisition of newly acquired pathologic knowledge; that the continued increase was due to clinical interest and greater diagnostic accuracy; and that the subsequent decline in the rate of increase was evidence that the lung cancer "epidemic" had been the result of improved investigative techniques and not of a progressive increase in the disease. On the basis of Farber's study in California more than 50 per cent of lung cancers still remain undiagnosed until autopsy suggesting that the millenium of diagnostic acumen is still far distant.

The pattern of lung cancer incidence in the United States based on mortality statistics paralleled that in Germany based on necropsy data. The meticulous records maintained by the pathologic institutes affiliated with large municipal hospitals provide comparative data to study the history of the disease in the same

* TABLE V shows decline in rate of increase in New York State, 1931-1960

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TABLE VI

LUNG CANCER IN EUROPEAN HOSPITALS

IN LATE 19th AND EARLY 20th CENTURIES

CITY	AUTHOR	YEARS	% TOTAL NECROPSIES	PERCENT INCREASE	% TOTAL CANCERS	PERCENT INCREASE
BERLIN						
Friedrichshain	Reichelman	1895-1901	----		3.80	
Hospital	Bieberfeld	1907-1916	----		6.0	60
	"	1917-1926	----		6.20	0
Neukolln	Kuhn	1909-1914	0.33		4.68	
Hospital	"	1920-1924	0.90	180	8.08	75
	"	1925-1929	1.83	100	10.63	32
Charité	Bejach	1904-1908	----		2.79	
Hospital	"	1909-1912	----		4.95	80
	Hanf	1922-1925	----		7.50	50
Moabit	Wahl	1917-1918	----		3.53	
Hospital	"	1923-1924	----		14.08	300
	"	1924-1925	----		16.45	17
	"	1925-1926	----		12.35	0
	"	1926-1927	----		13.10	6
CHEMNITZ						
Pathologic	Briese	1898-1916	0.46		4.51	
Hygienic	Schonherr	1919-1922	0.88	90	9.50	110
Institute	"	1923-1927	1.50	70	11.80	24
TROPPAU						
	Materna	1912-1914	0.11		2.08	
	"	1915-1917	0.35	250	7.14	240
	"	1921-1923	0.57	66	8.00	12
ZURICH						
	Probst	1906-1910	0.11		1.13	
	"	1911-1915	0.38	245	3.34	190
	"	1916-1920	0.59	55	6.12	83
	"	1921-1925	0.97	64	7.17	17
LEIPZIG						
Pathologic	Seyfarth	1900-1906	0.67		5.01	
Institute	"	1907-1913	0.90	50	----	
	"	1914-1918	0.01	12	11.23	120
	Schlesinger	1924-1929	1.02	0	13.20	18
GÖTTINGEN						
Pathologic	Feldner	1852-1879	0.05		0.62	
Institute	"	1880-1908	0.14	180	0.90	61
	Simross	1906-1912	0.45	220	2.59	190
	Engenolf	1921-1927	0.65	44	4.43	70

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TABLE VI
(continued)

LUNG CANCER IN EUROPEAN HOSPITALS

IN LATE 19th AND EARLY 20th CENTURIES

CITY	AUTHOR	YEARS	% TOTAL NECROPSIES	PERCENT INCREASE	% TOTAL CANCERS	PERCEI INCRE
BASEL						
Pathologic	Staehlin	1900-1911	----		2.10	
Institute	"	1912-1914	----		5.00	140
	"	1915-1923	----		4.90	0
DRESDEN						
Friedrichstadt	Reinhard	1852-1876	0.057		0.92	
Hospital	Wolf	1877-1894	0.36	530	----	
	Junghanns	1893-1912	0.66	83	6.46	600
	"	1913-1927	0.96	45	10.73	24
Johannstadt	Langbein	1902-1906	0.81		----	
Hospital	"	1907-1911	1.18	45	----	
	"	1912-1917	0.96	0	----	
	"	1918-1923	0.85	0	----	
HAMBURG						
Eppendorf	Kikuth	1889-1899	0.07			
Hospital	"	1900-1911	0.37	530	3.80	
	"	1910-1919	----		4.85	30
COLOGNE						
Augusta	Eichengrun	1902-1919	0.25		4.53	
Hospital	and	1910-1919	0.56	120	8.10	80
	Esser	1919-1926	0.81	30	9.17	13
PRAGUE						
	Holzer	1895-1899	0.05		0.78	
	"	1905-1909	0.18	260	2.24	190
	"	1915-1919	0.32	77	4.81	110
	"	1920-1924	0.60	88	7.98	66
MAGDENBURG						
	Homann	1906-1909	0.18		1.74	
	"	1910-1913	0.41	130	4.10	138
	"	1925-1927	0.60	46	5.29	30
HEIDELBERG						
Pathologic	Katz	1906-1910	0.70		----	
Institute	"	1911-1915	0.94	34	----	
	"	1916-1920	0.87	0	----	
	"	1921-1925	1.42	55	----	

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TABLE VI
(continued)

LUNG CANCER IN EUROPEAN HOSPITALS
IN LATE 19th AND EARLY 20th CENTURIES

CITY	AUTHOR	YEAR	% TOTAL NECROPSIES	PERCENT INCREASE	% TOTAL CANCERS	PERCE INCRE
RIGA						
Municipal	Hampeln	1876-1884	----		----	
Hospital	"	1885-1894	----		4.00	
	"	1895-1899	----		12.50	210
INNSBRUCK						
University	Sitsen	1869-1880	0.33		----	
Pathologic	"	1881-1890	0.47	42	----	
Institute	"	1891-1900	0.22	0	----	
	"	1901-1910	0.14	0	----	
	"	1911-1918	0.33	140	----	
	"	1919-1927	0.58	80	----	
	"	1926-1934	0.62	7	----	
ZWICKAU						
Charity	Lipschitz	1909-1913	1.00		5.40	
Hospitals	"	1914-1918	1.00	0	6.10	13
(Nat'l Research	"	1919-1923	1.90	90	11.30	85
Institute)	"	1924-1928	2.00	0	12.90	14
BUDAPEST						
Pazmany-Peter U.	Zalka	1894-1898	0.126		1.02	
St. Stephans	"	1904-1908	0.329	160	2.70	160
Hospital	"	1914-1918	0.420	30	3.35	24
MANCHESTER						
Royal	Dugid	1868-1885	0.24		----	
Infirmary	"	1886-1890	1.58	550	----	
	"	1891-1895	1.28	0	----	
	"	1896-1900	1.21	0	----	
	"	1901-1905	2.10	70	----	
	"	1906-1910	1.34	0	----	
	"	1911-1915	2.37	75	----	
	"	1916-1920	2.42	0	----	
	"	1921-1925	2.57	0	----	
LONDON						
St. Bartholomew's	Maxwell	1884-1888	0.40		3.91	
Hospital	and	1894-1898	0.96	140	7.83	100
	Nicholson	1904-1908	0.84	0	7.17	0
LEEDS						
General	Bonser	1891-1892	0.81		6.30	
Infirmary	"	1893-1897	1.05	30	7.42	18
	"	1898-1902	1.12	7	6.60	0
	"	1903-1907	0.86	0	4.95	0
	"	1908-1912	1.30	51	8.27	69
	"	1913-1917	1.27	0	7.73	0
	"	1918-1922	0.91	0	6.17	0
	"	1923-1927	1.17	29	7.97	30

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locality over a period of many years. TABLE VI illustrates the necropsy incidence of lung cancer in various European centers expressed as a percentage of total cancers and/or total autopsies.

The 4 major hospitals in Berlin showed a similar lung cancer necropsy experience. At the Friedrichshain there was a 60 per cent increase in the percentage of lung cancer to total cancer between the periods 1895-1901 and 1907-1916 and no increase between the latter and the period 1917-1926. The figures at Neukolin showed an increase of 180 per cent in the percentage of lung cancer to total autopsies between 1909-1914 and 1920-1924 and 100 per cent increase between 1920-1924 and 1925-1929. The respective figures for the lung cancer-total cancer ratio were a 75 per cent increase between the first two periods and a 32 per cent increase between the second and third periods. It is to be noted that despite the progressive increase in the autopsy and total cancer percentage of lung cancer, the rate of increase in both instances had begun to decline. At the Charité, the percentage of lung cancer to total cancer increased from 2.79 to 7.50 between 1904 and 1925 but the rate of increase declined after 1912.

The lung cancer data at Moabit showed a low percentage of total cancers in the period 1917-1918 and a rapid increase in the succeeding period. Between 1923 and 1927 the percentages exceeded many found in later decades. However, after the initial 300 per cent increase the rate dropped precipitously and continued at a low level. Peters combined the lung cancer data from the Moabit and Urban hospitals for the period 1895-1931. There were 27,858 autopsies; 3,957 carcinomas, and 313 lung cancers. In the period 1895-1922, the autopsy percentage was 0.7 per cent; in the

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period 1922-1927, it was 1.7 per cent; and in 1927-1931, it was 2.6 per cent. Between the first two periods, the rate of increase had been 140 per cent but between 1922-1927 and 1927-1931 the rate declined to 53 per cent.

The studies of Reinhard and Wolf made it possible to follow the lung cancer incidence in Dresden for more than 75 years. Both the autopsy and lung cancer-total cancer percentages increased greatly in the latter part of the 19th and early 20th centuries at the Friedrichstadt hospital. The increase continued for approximately 25 years and by 1927 the autopsy and total cancer percentages were higher than those of many comparable institutions. It is of considerable significance that the peak of the autopsy rate of increase was reached by 1894 and the peak of the total cancer percentage by 1912 followed by a sharp decline in succeeding years. At the Johannstadt hospital in Dresden the autopsy percentage declined after 1911.

Three decades of lung cancer history in Prague reveal a progressive decline in the rate of increase after 1909. In Zurich, Probst found the peak of increase in both autopsy and total cancer percentages in 1915 after which both fell sharply. The lung cancer-total cancer percentage in Basel increased to 1914 and then remained stationary until 1923 and in Cologne it declined after 1919. In Gottingen the greatest increase in autopsy and total cancer percentage occurred before 1912.

In those institutions in which the earliest data showed relatively high autopsy and total cancer percentages there was little subsequent change. At the pathologic institute of Heidelberg, the autopsy rate of increase showed no striking changes between 1906

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and 1925. In Zwichau, the autopsy incidence was high before 1913 and reached the peak by 1923 after which it remained level. The lung cancer-total cancer percentage also showed little increase after 1923.

The statistical studies at the General Infirmary in Leeds extended over 35 years and showed almost no increase in autopsy or total cancer percentage between 1891 and 1927. Starting with an autopsy incidence of 0.81 per cent and a total cancer incidence of 6.30 per cent the respective percentages reached 1.05 and 7.42 by 1897. The subsequent fluctuations in increase were minimal and in 1927, the autopsy and total cancer rates differed little from those in 1897. Throughout this period the autopsy rate at the hospital approximated 80 per cent adding considerably to the validity of the observations. It is apparent from the data that no increase in the incidence of lung cancer occurred between 1891 and 1927, a period which included the eras before and after the onset of heavy cigarette smoking.

The observations at the Royal Infirmary in Manchester covered more than half a century. The autopsy incidence was 0.24 per cent in the period 1868-1885 and reached 2.57 per cent in 1925. The greatest increase occurred before 1890 and after 1915, there was virtually no change. There was a level of sustained interest in lung cancer at St. Bartholomew's Hospital during the second half of the 19th century. The post mortem records date back to 1867 but Martin, the hospital pathologist, had already reported a case in the St. Bartholomew's Hospital Reports in 1865. There was a succession of contributions emanating from the hospital and Harris, in 1892, found 41 cases in the previous decade. In 1897

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West described the findings in more than 60 cases of primary lung cancer and a larger number of metastatic carcinomas and other intrathoracic neoplasms. There were no further studies on lung cancer in the St. Bartholomew's Hospital Reports for a great many years until Maxwell and Nicholson, in 1929, reviewed the necropsy material dating back to 1873. The findings were remarkable in that they revealed autopsy and total cancer percentages in the late 19th and early 20th centuries comparable to those prevailing in other institutions more than two decades later.

The pattern of incidence of lung cancer in the European hospitals closely resembled that which occurred in this country decades later. There was a sharp rise in the early years of the studies reflecting pathologic detection of the new disease followed by declining rates of increase as diagnostic criteria became firmly established. In localities with a long history of lung cancer recognition such as Chemnitz, Leipzig, Berlin, Dresden, Leeds, etc. the autopsy incidence and percentages of total cancers 40-50 years ago were comparable to those prevailing at the present time.

Necropsy Incidence of Lung Cancer

During the early decades of the 20th century the number of lung cancer cases diagnosed at necropsy increased rapidly in many European hospitals. This was generally interpreted as signifying an absolute increase; a concept that has been perpetuated to the present time. There were also dissenting opinions from contemporary observers, chiefly German investigators, who considered the increase "nur eine scheinbare" (apparent).

In 1901, Feilchenfeld, noted the rise in necropsy incidence

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in a study from the Urban Hospital in Berlin and attributed it to increased number of autopsies, the utilization of more precise techniques of examination, and interest in the subject by the pathologist, Benda. Karrenstein, in 1908, in a report from the University of Berlin stated that a rise in the incidence could not be properly evaluated because the previous public health statistics on lung cancer had been totally inadequate for comparison. He emphasized that refinements in histologic study had made it possible for the pathologist to recognize primary lung cancer much more frequently and, that in former years, the late complications of the disease such as pneumonia, abscess, and diffuse metastases often obscured the primary lesion.

Adler, whose publications on lung cancer spanned both the 19th and 20th centuries commented in his monograph, in 1912, "There seems hardly room for doubt that the increase in the percentage of lung cancers is to be attributed mainly to the increased attention paid to these types of tumor and the greater care and more extensive microscopic investigation with which autopsies are carried out at present." As early as 1896, he had maintained that lung cancer was far more prevalent in the United States than the impression created by medical textbooks or census reports.

The spate of statistical studies emanating from German pathologic institutes and those of other European countries continued for more than 3 decades with divided opinions as to whether the lung cancer increase was real or apparent. Staehlin, in a report from Basel in 1925 based on more than 20 years' observation concluded that no real increase had occurred. Breckwoldt, in 1926, analyzed the data from the Eppendorf and Barmbeck hospitals

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in Hamburg and found the increase only apparent, in both institutions. In 1927, Ferenczy and Matolcsy reported a tremendous increase in Vienna between 1896 and 1925 and commented that the number of cases escaping pathological detection had become progressively smaller with the passing years.

Sitsen, in 1935, reviewed the lung cancer material at the University of Innsbruck from 1869 to 1934 and concluded that lung cancer was no more frequent in the 20th century than it had been in the 19th century. He stated that many factors had contributed to the increase in necropsied cases among which he listed (1) more accurate examinations, (2) change in type of cases hospitalized, (3) change in the nature of the autopsy material with respect to sex and age distribution, and (4) selection of patients in the diagnostic clinics from larger segments of population including distant regions. One of the most significant comments was that the numerical increase in lung cancers over the years must be correlated with the entire autopsy experience of the particular hospital.

Willis recently stated, "The mistakes in pathological diagnosis which were common in the early years of the century are much less frequent now; but they are not wholly extinct." The criteria for the histologic diagnosis of primary lung cancer did not become common knowledge until well into the 20th century. It has already been pointed out that the recognition of the undifferentiated cell type which comprises a large proportion of lung cancers did not occur until 1926. The abrupt rise in necropsy incidence in varied localities during different periods of time

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suggests that the increase was due to acquisition of greater interest and/or pathologic knowledge rather than to successive waves of the "epidemic".

Harvey, in 1936, reviewed the records at the Royal Prince Alfred Hospital in Australia between 1910 and 1935 and reported 100 cases of primary lung cancer of which 19 had not been previously recognized. The erroneous necropsy diagnoses included tuberculosis, bronchiectasis, and duodenal ulcer. It is of significance that almost half of the lung cancer cases had been diagnosed during the last 5 years of the study. Pathologic experience is an important factor in the incidence of lung cancer at necropsy. Jaffé who had previously studied lung cancer in Vienna during the period 1915-1918 found the incidence of lung cancer to total cancers in excess of 11 per cent at the Cook County Hospital in Chicago in 1929-1934; during this period the incidence was less than 1.0 per cent at the University of Oregon and less than 2:0 per cent at the Vancouver General Hospital. In institutions such as St. Bartholomew's, Leeds General Infirmary, Manchester Royal Infirmary, and Edinburgh General Infirmary in which familiarity with lung cancer had been established in the late 19th century there was a sustained high rate of incidence for many decades.

Necropsy experience in the United States lagged considerably behind that of the German pathologic institutes and only a small number of lung cancer cases were reported in the first three decades of the century. Fischer's data on lung cancer statistics in the 1931 edition of Henke and Lubarsch included almost 4,000 cases of which only a very small percentage were derived from American reports. Weller, in 1913, contributed an excellent discussion on

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the pathology of lung cancer from the University of Michigan, but the study included only one case from his institution. In succeeding years, additional reports trickled into the literature from American institutions but none of a magnitude comparable to those from the European hospitals.

Lichty, reported 17 cases in 1926 and, in his article referred to 34 cases studied by Symmers at Bellevue Hospital and 23 cases by Randolph at the University of California. Freemont-Smith reported 18 cases at the Boston City Hospital between 1915-1929 and McCrae found 4 cases between 1924-1927 at the Jefferson Hospital. There were also necropsy reports of limited numbers of cases by Barron, Moise, Fried, and others. One of the larger reports was that by Fishberg, who found 36 cases at the Montefiore Hospital between 1916-1926; most of the cases had been treated previously for tuberculosis.

After 1930 there was a perceptible increase in the number of necropsied cases of lung cancer reported. The largest series was that of Jaffé from Chicago in 1935 which included 100 cases; there was also a study of 72 cases from Boston by King in 1938 and one of 92 cases by Halpert in 1940 from New Orleans. In 1942, King and Ford reported 158 cases from Baltimore and many studies have since been published with numbers of cases comparable or exceeding the earlier European reports.

The increase in lung cancer necropsies occurred in this country many years after it had occurred abroad because of the lag in interest and pathological experience. The only alternative explanation is that the "epidemic" took two decades to cross the Atlantic Ocean, an hypothesis which is untenable even if it includes

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exposure to cigarettes as an etiological factor; there was no significant variance between the onset of heavy smoking in this country and abroad. The same factors operated in both areas to produce an increase in the number of necropsied cases, namely, selectivity in hospital admissions, increased facilities for diagnosis and treatment, and progress in histologic recognition.

King, in 1938 analyzed the lung cancer material at the Massachusetts General Hospital. There were 475 cases with the first case diagnosed at necropsy in 1842 and the second in 1856, the latter reported in the Boston Medical and Surgical Journal by Ellis. Between 1875 and 1914 there were 45 additional cases and after 1920 there was a sharp increase in incidence. Of the 475 cases, the diagnosis was confirmed in 158 by autopsy, biopsy or exploratory thoracotomy. King attributed the increase in the later years to the interest in diagnosis and therapy which had significantly influenced the nature of the admissions to the hospital. The widespread utilization of the roentgen examination had yielded an increased number of cases which had been referred to the hospital for possible surgery. A similar observation was made by MacCallum in 1930 when he noted that the increase in lung cancer at Johns Hopkins Hospital had occurred shortly after expansion of diagnostic facilities.

Considerable progress had been made in the pathology of lung cancer in the past half century but diagnostic errors are still being made. Funk, in 1930, reported a case in which the diagnosis of lung cancer had been established on the basis of bronchoscopic biopsy but autopsy revealed a primary cancer of the pancreas. Three similar cases were described by Leach and there were also reports by

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Maytum, Freedlander, and Campagna of cases diagnosed as lung cancer on the basis of bronchoscopic biopsy but subsequently found to have primary cancers in the kidney, ovary,and rectum, respectively. King and Castleman reported in 1943 that 18 per cent of pulmonary metastases had bronchial invasion.

A diagnosis established by bronchoscopic, lymph node or thoracotomy biopsy may be erroneous without autopsy confirmation. Metastatic tumors in the lungs may present the same histologic features as primary lung cancer thus leading to an exaggeration of the incidence of the disease. Inasmuch as 30-40 per cent of carcinomas have pulmonary metastases, the frequency of the mistaken diagnosis may not be insignificant.

Clinical Diagnosis of Lung Cancer

The physical examination and the cytological study of the sputum provided the only means of clinical diagnosis of lung cancer until the end of the 19th century. Shortly after Roentgen's discovery attempts were made to utilize the X-ray for examination of the chest and diagnoses confirmed by necropsy were reported in Germany by Weinberg, in 1901, and Otten, in 1906. In the United States, Packard successfully correlated X-ray findings with clinical manifestations in 1918. Widespread adoption of the X-ray examination of the chest was delayed for almost a decade because of technical problems and hazards which were ultimately resolved by the Coolidge tube and shock-proof equipment.

The second major contribution to clinical diagnosis was the introduction of the bronchoscope by Killian, in Germany, in 1898. Unwarranted anxieties concerning contra-indications limited the utilization of the bronchoscopic examination for more than 3

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decades. Smithers stated that only one bronchoscopy had been performed at the Brompton Hospital before 1925 whereas more than 800 were being done annually in 1952.

The greatest impetus to bronchoscopy was provided by Jackson who had demonstrated in Philadelphia since 1917 that the procedure was practicable and of invaluable assistance in clinical diagnosis. By 1930, he had diagnosed 486 cases of lung cancer and his efforts inspired interest in bronchoscopy all over the world. Bronchoscopic examinations were usually performed by otolaryngologists for many years but this function was subsequently assumed by thoracic surgeons thereby increasing the number of procedures considerably. It is very significant that as a result of bronchoscopy another "new disease" was discovered. Although pulmonary tuberculosis had been known since the time of Hippocrates, endobronchial involvement was not recognized until after 1930, following which it was discovered to be one of the commonest complications of the disease.

The third major contribution to clinical diagnosis was exploratory thoracotomy. Considerable interest in surgical therapy existed in Germany in the first decade of the century and Seydel, in 1910, reviewed the indications for thoracic surgery and described operations performed by Küttner, Lenhartz, and Garrè. Adler, in 1912, referred to surgical experiences of Sauerbruch, Friedrick, Brauer, and Ders, in Germany and Meyers, in this country. Despite the high operative mortality rate, efforts at surgical extirpation of lung cancer persisted and finally culminated in the successful pneumonectomy by Graham, in 1933. Subsequent advances in technique, anesthesia, and post-operative

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management led to wider utulization of resectional surgery and shortly after 1940 thoracotomy became a routine procedure in most medical centers. The marked reduction in operative mortality encouraged the use of exploratory thoracotomy in obscure cases. In 1949, Johnson reported a series of 123 lung cancers of which almost 50 per cent had been diagnosed only after surgical exploration.

The fourth major contribution in clinical diagnosis was the Papanicolaou staining technique described in 1943. Originally devised for gynecological investigation it was soon applied to the examination of sputum and bronchial aspirates. Within a few years the "Pap" smear had become a routine procedure in all hospitals. Many studies on the cytological examination of the sputum, using various stains, had preceded Papanicolaou's method but none had produced a comparable degree of cell differentiation.

There were other ancillary procedures which contributed to the clinical diagnosis of lung cancer. One of the most important was the routine use of sputum and gastric cultures for tubercle bacilli in cases diagnosed as pulmonary tuberculosis but with negative findings on direct smear. A negative culture became, in many instances, an indication for investigation for lung cancer. Other diagnostic techniques which facilitated the detection of lung cancer were cytological examination of pleural effusions and lymph node biopsy.

It is to be emphasized that the major procedures in the clinical diagnosis of lung cancer came into widespread use within the past 3 decades. This has resulted in the recognition of increasing numbers of cases most of which would have not been diagnosed if the present techniques were not generally available.

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Bronchoscopy has become a routine procedure in all institutions; most adults have been subjected to one or more X-ray examinations of the chest either in military service, industry, hospital admission, health survey, or, private medical practice; exploratory thoracotomy, once a procedure of last resort, is now a common form of diagnostic investigation; and sputum specimens are being submitted to laboratories more often for examination for cancer cells than for tubercle bacilli.

Separately and collectively, the wide use of these diagnostic measures has been reflected in a general rise in the clinical and necropsy incidence of lung cancer during the past few decades. Willis, contrasted the modest increase in the necropsy incidence of lung cancer in the period 1929-1950 in England with the tenfold increase in registered deaths and inferred that practically all of the increase could be attributed to better clinical diagnosis, - an observation that has been often repeated by those familiar with the long history of the disease.

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Summary

1. Hundreds of articles, theses, and dissertations in the English, French, and German literature attest to the prevalency of lung cancer in the 19th century.
2. The sex and age distribution of lung cancer was found to be similar in the eras before and after the onset of heavy cigarette smoking.
3. The sex ratio favoring the male continued to increase despite the prodigious consumption of cigarettes by females.
4. The rate of increase of lung cancer showed a similar pattern of rapid rise followed by progressive decline in both necropsy and mortality statistics.
5. The continuing decline in the rate of increase suggests that the rise in lung cancer incidence resulted from improved investigative techniques rather than from an absolute increase of the disease.
6. The increased necropsy incidence of lung cancer in many hospitals was a reflection of increased pathologic knowledge and changes in autopsy material based on selective hospital admissions.
7. In institutions with a long history of lung cancer recognition the autopsy incidence and percentage of total cancers showed no remarkable changes over a period of many decades.
8. The increased incidence of lung cancer is the result of diagnostic accuracy made possible by techniques that were introduced or perfected within the past few decades.

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Source: https://www.industrydocuments.ucsf.edu/docs/ktyk0000

LUNG CANCER IN THE 19th CENTURY

A

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